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Barry E. Yarbrough, M.D. and Roger W. Hubbard, Ph.D

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This chapter in the 2nd edition of the Management of Wilderness and Environmental Emergencies, provides background material in the following areas: Physics of heat transfer, physiology of human body temperature regulation, the CNS interface between thermosensors and thermoregulatory effectors, skin blood flow and vasodilation, and acclimatization. The heat illnesses coverage includes information on predisposing factors, thermometry, and fever versus hyperthermia. The review of heat illnesses includes heat cramps, heat edema, heat syncope, heat exhaustion and heat stroke. Treatment coverage includes the differential diagnosis, classical versus exertional forms of heatstroke, the systemic and cellular approach to pathophysiology which includes an organ by organ analysis. The specifics of treatment provides insight to electrolyte abnormalities, acid-base abnormalities and the ABC's of therapy including cooling, modalities, adjunctive measures and prevention. Keywords: Heat Stress Physiology

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HEAT-RELATED ILLNESSES

Barry E. Yarbrough, M.D.*

Assistant Professor of Surgery and Medicine

Vanderbilt University Medical Center

Nashville, Tennessee

Roger W. Hubbard, Ph.D.

Director, Heat Research Division

U.S. Army Research Institute of Environmental Medicine

Natick, Massachusetts

*The authors acknowledge the scholarly review and comments offered by L.E. Armstrong, R.P. Francesconi, and C.B. Wenger.

INTRODUCTION

Man is a tropical mammal with a body better suited to tolerate and adapt to heat than to cold stress. Despite this ability, man has been plagued by heat illness throughout recorded history. The Old Testament describes a young man's death after laboring in hot fields during harvest (II Kings 4:18-20). The ancient Greeks described a disease ("siriasis") which resembles heat stroke after the dog star Sirius which accompanies the summer sun.[142] Many military campaigns have been lost due to lack of heat acclimatization and subsequent heat illness. A Roman army in Arabia was decimated by heat in 24 BC.[142] King Edward and his metal-armored crusaders allegedly lost the final battle of the Holy Land against the well-adapted and well-ventilated Arab horsemen because of heat illness.[167] Modern military organizations continue to encounter heat illness because of the requirement to train unacclimatized men by means of forced heavy physical exercise. The United States Army reported at least 125 deaths from heat stroke during basic training in the years 1941-1944.[110] Athletes are also prone to develop heat illness. Between 1961 and 1971, 46 American football players died of heatstroke.[117] Heatstroke is third only to head and spinal cord injuries and heart failure as a cause of death among American athletes.[89]

When environmental heat stress is maximal, strenuous exercise is not required to produce heat illness. In 1956, 123 of 146 British soldiers imprisoned in the "Black Hole of Calcutta" on a sweltering summer night succumbed to heat stroke.[142] The civilian population, particularly the elderly and poor (lacking adequate air-conditioning

and nutrition), and those with pre-existing disease, are prone to heat illness during environmental extremes. A heat wave in Peking caused 11,000 deaths in 1743.[88] During the heat wave years 1952-1955 and 1966, an average of 820 annual heatstroke deaths were reported in the United States, as compared to 179 deaths per non-heat wave year. It is estimated that at least ten times as many heat-aggravated illnesses due to myocardial infarction, cerebrovascular accident, and other causes occurred during these years.[40] Despite recent advances in prevention and treatment of heatstroke, thousands of persons, mostly elderly, died during a heat wave in Greece and Italy in the summer of 1987.

To prevent and appropriately manage heat illness, the clinician must understand thermal stress and human pathophysiology. This chapter reviews the physics of heat transfer, physiology of human thermoregulation, pathophysiology of heat illness, and current concepts of prevention and management of heat illness.

PHYSICS OF HEAT TRANSFER

Heat Production

Humans may be considered biochemical "furnaces" which burn food to fuel a complex array of metabolic functions. These chemical reactions consume substrate, generate usable energy, and produce by-products which must be eliminated for continued operation of the system. Water and carbon dioxide are produced and eliminated in large quantities, as are urea, sulfates, phosphates, and a variety of other chemical products. All of these reactions are exothermic and combine to produce the basal metabolic rate. This amounts to approximately 50-60

kcal/hour/m^2 of body surface area, or 100 kcal/hour for a 70 kg person (the "average man").

Heat production may be increased 10-20 fold by strenuous exertion.[145] Rectal temperatures of 40-42° C have been recorded in trained marathon runners.[25,125,201] Other factors, including hyperthyroidism and sympathomimetic drug ingestion, may dramatically increase heat production. Environmental heat adds to the heat load and interferes with heat dissipation. There are four mechanisms of heat transfer: conduction, convection, radiation, and evaporation.

Conduction

Conduction is transfer of heat energy from warmer to cooler objects by direct physical contact. Air is a good insulator; therefore, only approximately 2% of body heat loss is by conduction. In contrast, the thermal conductivity of water is 32 times that of air;[143] therefore, temperature loss during cold water immersion is rapid (see Chapter 3).

Convection

Heat loss to air and water vapor molecules circulating around the body is termed convection. As ambient temperature rises, the amount of heat dissipated by convection becomes minimal, and once air temperature exceeds mean skin temperature, heat is gained by the body. Convective heat loss varies directly with wind velocity. Loose-fitting clothing maximizes convective (and also evaporative) heat loss.

Radiation

Radiation is heat transfer by electromagnetic waves. Although radiation accounts for approximately 65% of heat loss in cool

environments, it is a major source of heat gain in hot climates. Up to 300 kcal/hour can be gained from radiation in persons directly exposed to the hot summer sun.[47] Black skin absorbs approximately 20% more heat than does white skin,[78] but adds protection from the harmful ultraviolet component of solar radiation. It should be noted that black skin may severely burn from overexposure to the sun.

Evaporation

Evaporation is conversion of a liquid to the gaseous phase. Pertinent to humans, this is accompanied by the loss of 0.58 kcal/cc of water evaporated. As ambient temperature rises, evaporation becomes the dominant mechanism of heat loss. Panting mammals such as dogs have an oropharyngeal countercurrent flow mechanism (carotid rete) which results in selective cooling of the brain. In humans, respiratory and countercurrent mechanisms are minimal sources of heat loss and the dominant mode of cooling in hot conditions is evaporation of sweat from the skin.

PHYSIOLOGY OF HUMAN BODY TEMPERATURE REGULATION

Regulation of human body temperature may be conceptualized as three distinct functions. Sensor mechanisms detect changes in body temperature. Thermal signals are relayed from central and peripheral locations to a central integrative area, which directs various effector organs to increase or decrease heat loss appropriately.

THERMOSENSORS

Historically, most physiologists believed that all sensory input

for thermoregulation originated from warm and cold receptors located in the skin. This belief was challenged in the 1950's when devices to measure heat loss were developed and attempts made to correlate the rate of heat loss with skin temperature.[15] In an environment where air temperature exceeds skin temperature, the dominant mode of heat loss is evaporation of sweat. When Benzinger[15] measured skin temperature, heat loss, and sweating rate, no correlation could be found. Likewise, rectal temperature correlated poorly with rates of sweating and heat loss. However, when measuring tympanic membrane temperature, sweating and vasodilation increased linearly above a "set point" temperature, which varied slightly among individuals but was always around 37° C (98.6° F).[17] In 1961, Nakayama[128] described thermosensitive neurons in the preoptic area of the anterior hypothalamus (PO-AH) and Hellon[62] observed that these neurons fired when their sensory reception threshold, or set point, was exceeded. The central location of this thermosensor does not explain the correlation of heat loss with tympanic membrane, but not rectal, temperature. Rather, the brain, which is well perfused relative to its mass, responds rapidly to changes in blood temperature. Tympanic membrane temperature responds less rapidly but correlates well enough to provide a better index of the change in brain temperature than does rectal temperature.

Skin temperature is believed to have an effect on sweating and heat loss, since a person resting in a warm environment with elevated skin temperature initiates sweating, even though core temperature remains constant.[124] This is presumed to be a centrally-mediated effect, based on the observation that elevated skin temperature

influences the effector response even if the skin temperature is constant at a distant site where the response is measured.[192] There is evidence that local heating accelerates sweat production in a particular area, probably by facilitating transmitter release at the neuroglandular junction and augmenting glandular responsiveness.[133] Thus, both central and peripheral mechanisms cause sweating when skin temperature is elevated. Conversely, cooling the skin during exercise has been shown to inhibit sweating.[16] Changes in core temperature seem quantitatively more important and have been estimated to be 10 times more potent in producing heat-dissipating responses than are skin temperature changes.[151] It is likely that other thermosensors located in the spinal cord,[181] limb muscles[74] and perhaps elsewhere in the body participate in thermoregulation.

THE CNS INTERFACE BETWEEN THERMOSENSORS AND THERMOREGULATORY EFFECTORS

The CNS must interpret information received from thermosensors and in order to properly instruct thermoregulatory effectors. Whether the "set point" which keeps our body temperature within such a narrow range is a property of an anatomic structure within the CNS or a concept developed to explain a complex system lacking a single central control center is currently disputed.[171] Some investigators doubt the existence of a central integrative mechanism and postulate that the set point is a property of genetically-fixed activity/temperature properties of warm and cold sensors[185] which modulate the intensities of heat production and heat loss effectors. However, considerable evidence suggests the existence of a central integrative mechanism at

the spinal cord and/or hypothalamic level.[49,193] The concept of a central thermostat, or set point, which shifts all effector thresholds in the same direction provides a conceptual framework which fits a variety of clinical situations. For example, fever, the daily circadian rhythm of temperature variation, and the 0.5° C difference in rectal temperature following ovulation seem to be variations in a thermal set point.

There are also various non-thermal stimuli which affect thermoeffector responses. During exercise, rapid (10-20 minutes) decreases in central blood volume occur due to several mechanisms, including osmotic loss of plasma water into working muscle tissues,[126] accompanied by peripheral vasodilation and orthostatic pooling. Sweating causes hypotonic fluid loss, which left uncompensated, exacerbates hypovolemia and produces hyperosmolarity. Reduced forearm sweating and vasodilation have been observed in severely dehydrated subjects during exercise in a warm environment.[127] Although the effect of dehydration on thermoregulation is controversial, the preservation of central volume is a potent homeostatic drive in man and may alter or even override heat dissipation effectors which would further embarrass circulating blood volume.

THERMOREGULATORY EFFECTORS

In a warm environment, the evaporation of sweat from skin is the most important mechanism of heat dissipation. Heat loss from the skin by convection and radiation is maximized by increased skin blood flow (SkBF), which also carries heat convectively from the core to the

surface. However, the main role of elevated SkBF in a warm environment is to deliver the heat necessary to evaporate sweat.

SWEATING

There are two types of sweat glands in humans, apocrine glands and eccrine glands. Apocrine glands are concentrated in the axillae and produce milky sweat rich in proteins and carbohydrates.[1] These apocrine glands are adrenergically innervated and respond to emotional distress as well as to heat. The majority of glands producing "thermal sweat" are eccrine glands. These are 1-3 mm tubular glands distributed over the entire body surface area, with the most dense concentration on the palms and soles. An adult carries 2 to 3 million eccrine glands, innervated primarily by cholinergic effectors of the type. Eccrine sweat is a colorless, odorless, devoid of protein, and in excess of 99.5% water by weight.[1] Eccrine sweat glands actively resorb sodium dependent on salt intake and aldosterone secretion. The secretory capacity of sweat glands is prodigious; one gram of sweat glands can produce 250 g of sweat daily.[97] Persons engaged in physical exercise in hot climates commonly lose 1-2 liters of sweat per hour, although loss of 4 liters/hour for short periods of time has been reported.[146] Cooling is achieved by evaporation from the body surface; sweat which drips from the skin does not cool the body and sweat evaporated from clothing is considerably less efficient. Each liter of completely evaporated sweat consumes 580 kcal of heat and cools the body by this amount. The ability of the environment to evaporate sweat is termed "atmospheric cooling power" and varies primarily with humidity, but

also with wind velocity. As humidity approaches 100%, evaporative heat loss ceases. The major effect of wind in humid environments is attained at a velocity of 0.5-5 m/sec; higher wind velocities do not appreciably increase cooling.[18]

SKIN BLOOD FLOW AND VASODILATION

The normal response to heat stress is cutaneous vasodilation and compensatory vasoconstriction of the splanchnic and renal vascular beds. Skin blood flow (SkBF) rates of 8 L/min, accounting for 60% of total vascular conductance, have been observed in supine, resting individuals subjected to heat stress.[150] This impressive increase occurs through active sympathetic vasodilation;[44] although the neurotransmitter is currently unidentified, it may be linked to sweating. Onset times of sweating and vasodilation are nearly simultaneous[202] and vasodilation is absent in skin congenitally or pathologically lacking sweat glands.[21] Given the impressive SkBF rates which can be generated, it is not surprising that cardiovascular and baroreceptor reflexes are also involved in regulation of SkBF. As far as is known, non-thermal or baroreceptor effects are mediated only by adrenergic vasoconstrictor fibers. The relative contribution of thermal and non-thermal regulators during heat stress remains controversial.[151]

ACCLIMATIZATION

Acclimatization is natural adaptation to a warm environment; acclimation is adaptation following exposure in an artificial

environment. Daily exposure to work and heat causes acclimatization over a period of 10-14 days.[196] This is characterized by an earlier onset of sweating (at a lower core temperature), increased sweat volume, and lowered sweat electrolyte concentration.[38] Under ordinary circumstances, an untrained person may lose up to 1 liter of sweat per hour. As acclimatization proceeds, the sweat sodium concentration drops from approximately 65 mEq/liter to as low as 5 mEq/liter,[112] while the volume increases to as much as 3-4 liters/hour.[146] The electrolyte concentration often varies with the collection procedure, but sodium decreases from 30-50 mEq/liter are not uncommon. Volume must be replaced in order to prevent symptomatic hypovolemia. Prolonged acclimatization may eventually produce diminished sweat production in response to a given workload, due to enhanced sweating efficiency (earlier onset and better distribution) and lowered central drive induced by physical training.[2] Training does not improve "metabolic efficiency."

The cardiovascular system plays an important role in acclimatization and endurance training.[5,169] Peripheral vasodilation occurs earlier and in greater magnitude in trained individuals, but subsides after several days. Heart rate is lower and associated with a higher stroke volume, generally with no change in cardiac output. These cardiovascular changes are largely due to a 10-25% expansion of plasma volume which occurs with both exercise and heat acclimatization.[5] Other physiologic changes include earlier release of aldosterone from the adrenal cortex, although acclimatized individuals generate lower plasma levels of aldosterone during exercise-heat

stress. There may be total body potassium depletion of up to 20% (500 mEq) by the second week of acclimatization as a result of both sweat and urinary losses coupled with inadequate oral repletion.[87] Physical work and heat exposure are powerful stimuli to growth hormone release.[134,158] Growth hormone causes salt and water retention; some postulate that its action may be as important as aldosterone in acclimatization.[94]

There are many similarities between thermoregulatory responses to heat and endurance training. In both, there is increased sweat rate at the same body temperatures, decreased heat storage, decreased core temperature at given workloads, and expanded plasma volume. Unacclimatized marathon runners have improved heat tolerance, thus highly trained, but heat-unacclimatized individuals may not exist.[5] The converse is also true; heat acclimatization offers cardiovascular advantages for subsequent work. Some exercise is necessary to maximally increase plasma volume; this has been estimated to be a 40-50% thermal factor and 50-60% exercise factor.[32] To maintain heat and exercise-induced adaptive responses, heat exposure needs to continue intermittently at four-day intervals; plasma volume decreases considerably within one week in the absence of heat stress.[5] Still, the parallels between heat acclimatization and physical training are not strict, as evidenced by the fact that there are instances where improved aerobic power measured as VO_2 max is accompanied by a moderate decrease in heat tolerance.

HEAT ILLNESS

Predisposing Factors

The basic mechanisms which produce heat illness are increased heat production, decreased heat dissipation, and salt and water depletion, usually in combination. Since evaporation subsequent to sweating and increased peripheral blood flow is the primary means of heat dissipation, anything which interferes with these effector responses (eg, a humid microclimate) predisposes an individual to heat illness.

Under heat stress, cardiac output must increase significantly to provide increased peripheral blood flow. Persons with cardiovascular disease are not able to develop or accommodate this increase.[23] Dehydration, particularly hypernatremic, increases body temperature at rest by increasing the work of the celluiar sodium-potassium ATPase pump, which accounts for 20-45 percent of basal metabolic rate.[39,123] The intestine is a major site of electrolyte resorbtion; heatstroke related to fluid and electrolyte loss from gastroenteritis has been reported.[77] Virtually any chronic disabling disease can predispose to heat illness; an example is diabetes mellitus, in which both neurovascular and cardiovascular systems may be impaired.

Interference with sweating occurs in a variety of situations. Occlusive, non-vapor permeable clothing hinders evaporative and convective cooling.[11] Various skin diseases, including miliaria (prickly heat rash), extensive burns, scleroderma, ectodermal dysplasia, and cystic fibrosis are all risk factors. A fatal case of heat stroke was described in an elderly diabetic who had obstructive periductal lymphocytic sweat gland infiltration.[19]

Increased heat production causing heat illness most often

accompanies strenuous exercise in a hot or humid environment. The amount of energy expended during various activities is shown in Table 1. Several endocrine states, including thyroid storm and pheochromocytoma, dramatically increase heat production. Heat stroke often follows surgical removal of insulinomas;[66,183] the explanation remains unknown. Febrile illnesses[199] and delirium tremens are also risk factors.

Other risk factors for heat illness include obesity,[61] fatigue,[11] lack of sleep,[85] and alcoholism (Kilbourne ibid). Infants are at increased risk for heat stroke, possibly because of their relatively large body surface area/weight ratio and inability to control environmental stresses. A high surface area to weight ratio is an advantage when skin temperature is higher than ambient temperature. In spite of their higher surface area/weight ratio, children produce more metabolic heat per pound of body weight, sweat less, and direct proportionately less blood flow to skin than do adults. Infants are more easily dehydrated via urination and are less able to drink ad libitum. Persons with a history of heat stroke, with or without an inherent aberration which predisposed them to the prior episode, are at increased risk of a repeat episode.

A variety of synthetic drugs and natural ingestions have been implicated in the development of heat illness. Anticholinergic drugs block sweating and are the major offenders. These include atropine,[29] antiparkinsonian drugs such as benztropine mesylate,[106] and chemicals in plants such as Datura (Jimson weed) and Belladonna species.[55] Other medications with anticholinergic effects predisposing to heat illness

include phenothiazines,[8] tricyclic antidepressants, particularly if taken with MAO inhibitors,[108] and antihistamines.[52] Salicylates, used clinically as antipyretics, uncouple oxidative phosphorylation and produce hyperthermia if taken in large quantities[160] or in standard doses during exercise.[200] Overdoses of sympathomimetics, such as amphetamines, may cause fatal hyperpyrexia.[48] Rare cases of heatstroke have been reported in association with LSD[45] and methyldopa.[138] Alcoholism significantly increases risk for heat stroke.[43,85] The reasons for this remain unclear. Some authors cite enhanced absorption of an external heat load (from water immersion or water-perfused suits) due to alcohol-induced vasodilation as the explanation;[25] however, peripheral vasodilation is also an important mechanism for heat dissipation. Alcohol inhibits antidiuretic hormone and thus induces a relative dehydration, which may contribute to development of heat stroke.[85]

Certain patients undergoing general anaesthesia rapidly develop severe hyperthermia, muscular rigidity, and acidosis. A variety of anesthetics have been involved, but halothane, combined with succinylcholine, is the major offender. This syndrome, termed malignant hyperthermia, is due to a genetically determined instability of skeletal muscle sarcoplasmic reticulum which allows inappropriate intracellular calcium release.[129] Increased myoplasmic calcium causes numerous heat-generating reactions, including activation of myosin ATPase, which hydrolyzes ATP to ADP plus phosphate and heat.[22] These reactions explain clinical muscle rigidity, hyperphosphatemia, and hyperthermia. Drugs which lower myoplasmic calcium, such as

dantrolene, are effective in prevention and treatment of malignant hyperthermia.[95] Once the syndrome has developed, immediate cessation of anaesthesia and rapid cooling to correct hyperthermia are essential. Malignant hyperthermia differs distinctly from exertional heat illness; dantrolene has no proven efficacy in treating the latter.

Neuroleptic malignant syndrome is a disorder induced by antipsychotic medications, usually haloperidol, characterized by muscular rigidity, severe dyskinesia or akinesia, hyperthermia, tachycardia, diaphoresis, dyspnea, dysphagia, and urinary incontinence.[26] Although the muscular rigidity and hyperthermia are reminiscent of malignant hyperthermia, the putative mechanism is different. It is postulated that dopamine receptor blockade in the corpus striatum produced by haloperidol and similar drugs produces severe muscle spasticity and dystonia, leading to overproduction of heat. Haloperidol also causes suppression of thirst recognition, which further exacerbates the problem.[94] Rhabdomyolysis has been described and death may occur due to hyperthermia and exhaustion. Because sustained muscular contraction of dystonia is associated with sarcolemmal depolarization and elevated myoplasmic calcium levels, dantrolene therapy has been suggested; several cases of its efficacy have been reported.[33]

THERMOMETRY

The body may be thought of as a series of thermal "shells", layered over a central core. While the temperature of the most superficial shells varies dramatically with environmental temperature,

core temperature is maintained within a narrow range by the thermoregulatory mechanisms discussed previously. Since core temperature largely determines the body's response to thermal stress, clinical decisions in heat illness should be based upon this measurement. Unfortunately, most standard measurements of body temperature vary significantly from actual core temperature. Oral thermometry is affected by mouth-breathing and is a poor approximation. Rectal thermometry is less variable, but responds to changes in core temperature slowly. Thermistors which are inserted 15 cm into the rectum offer continuous monitoring of temperature and less variability, and although slower than tympanic temperature readings, are not biased by head skin temperature. If a patient has been instrumented with a Swan-Ganz catheter, pulmonary arterial temperature may be measured precisely with a thermistor catheter. This reading may be approximated closely by one from an esophageal thermistor positioned adjacent to the heart, which is usually less difficult than inserting an endotracheal or Ewald tube. Many studies on hyperthermia have utilized tympanic membrane temperature. The outer surface of the tympanic membrane is supplied by a branch of the maxillary artery. Because the inner surface of the tympanic membrane is surrounded by a vascular circle which anastamose with terminals of the caroticotympanic artery (a branch of the internal carotid artery), it provides a measurement of the temperature monitored by the hypothalamic thermoregulatory center. However, placement of a tympanic temperature sensor may be difficult in an uncooperative patient. Recently-developed and commercially available infrared thermometers do not physically contact the tympanic

membrane and facilitate a reading, but may be adversely affected by adjacent skin temperatures. Also, cooling one side of the face selectively lowers tympanic membrane temperature on that side. Esophageal thermometry is state of the art.

Fever versus Hyperthermia

Elevations of body temperature can occur as a result of several different mechanisms. One such mechanism is fever, whose pathophysiology differs from that of other identifiable causes of temperature elevation. It is both diagnostically and therapeutically important to understand fever and to identify those suffering from a febrile response as opposed to exercise hypothermia.

Fever is caused by pyrogens released by bacteria or viruses (exogenous pyrogens), or from cells undergoing autolysis after having participated in phagocytic activity (endogenous pyrogens).[177] Circulating pyrogens reach the thermoregulatory control center in the preoptic area of the anterior hypothalamus and act there to reset the thermal set point at a new level above 37°C, the "normal setting". Considerable data suggest that pyrogens act by inducing synthesis of prostaglandins in the region of the thermoregulatory center. Injection of an E-series prostaglandin into the cerebral ventricle of the cat and rabbit produces rapid and profound hyperthermia.[118] Prostaglandin E_2 is a normal constituent of hypothalamic tissue and activates heat production mechanisms in a manner similar to hypothalamic injection of pyrogen.[4,65] Prostaglandin inhibitors such as salicylates diminish or prevent the increase in cerebrospinal fluid prostaglandin concentration

concomitant with reduction of body temperature.[42] However, in other experiments, prostaglandin antagonists failed to block the hyperthermic effect of leukocyte pyrogen, raising the possibility that leukocyte pyrogen directly affects cells in the central nervous system.[35] The precise role of prostaglandin in fever remains under investigation.

Under most circumstances, temperature elevation is not a significant problem and therapy is directed at the underlying disease state. Fever has not been demonstrated to cause primary pathologic or physiologic damage to the organism and does not require primary emphasis in the therapeutic regimen.[177] However, if temperature-related physiologic changes, such as febrile seizures or tachycardia in a patient with marginal cardiac reserve, compromise the individual, temperature must be artificially regulated.

With fever, the temperature protected by the thermoregulatory center is elevated above normal. Once this temperature is established, the thermoregulatory center utilizes all available heat regulatory servomechanisms to maintain the new temperature. Febrile patients have a new thermopreferendum, or preferred ambient temperature.[177] Thus, a patient with a fever in an environment in which he was previously therma- comfortable begins to feel cold and chooses a warmer environment. This behavioral drive is coordinated with autonomic mechanisms such as shivering to increase body temperature to the new set point. This effect is most marked at the onset of fever, in the so-called "chill phase".

The definition of fever as a subset of hyperthermia has important physiologic and clinical implications. Because fever is the product of

a molecular interaction which establishes a new physiologic thermal set point, therapeutic ministrations which utilize external means to lower temperature are opposed by body mechanisms which attempt to maintain the new set point. Thus, attempts at whole body cooling produce violent shivering and discomfort. Therapy which utilizes agents to block the causative molecular interaction is the most rational and clinically effective approach. Aspirin is the time-honored means of combatting fever. This agent apparently blocks the action of the pyrogen at hypothalamic receptor sites, either directly or indirectly, through inhibition of prostaglandin synthesis.[42] Other agents with similar antipyretic properties include acetaminophen, indomethacin, ibuprofen, and other newer non-steroidal anti-inflammatory compounds. The conclusion which corroborates clinical and empirical observations is that aspirin works well to control fever but does not work and should not be used to control environmental hyperthermia.
58,167,177

MINOR HEAT ILLNESS

Heat Cramps

Heat cramps are brief, intermittent, and often severe muscular cramps occurring typically in muscles which are fatigued by heavy work. Steel workers, coal miners, sugar cane cutters, and boiler operators are among the most commonly reported victims.[179] Heat cramps tend to occur after exercise when the victim has stopped work and is relaxing.[94] In this respect, they differ from the cramps experienced by athletes during exercise which tend to last for several minutes, are relieved by massage, and resolve spontaneously. Heat cramps are

occasionally confused with hyperventilation tetany which may occur during heat exhaustion.[73] The latter syndrome may be distinguished by the presence of carpopedal spasm and parasthesias in the distal extremities and perioral area. If accompanied by systemic symptoms, heat cramps may be part of salt-depletion heat exhaustion, discussed below. No cases of rhabdomyolysis or resultant renal damage have been reported with isolated heat cramps.

Heat cramps are suffered by persons who produce large amounts of thermal sweat, and subsequently drink water without adequate salt. Many authors claim that heat cramps occur mostly in heat-acclimatized individuals,[94,25] while others[98,111,167] indicate that acclimatization produces resistance to heat cramps. Talbot[179] found that the maximal incidence of heat cramps was during the first several days of work in a hot environment.

Heat cramps seem to be related to salt deficiency. Several steel mills virtually eliminated heat cramps in their employees by encouraging salt consumption.[179] Anecdotal reports from Germany and England indicate that laborers salt their beer to successfully prevent heat cramps. Heat cramp victims exhibit hyponatremia, hypochloremia, and low urinary sodium and chloride levels.[102,179] Finally, heat cramps are usually rapidly relieved by salt solutions. Mild cases with concurrent hypohydration may be treated orally with 0.1%-0.2% salt solution (2-4 10-grain salt tablets [56-112 mEq] or 1/4-1/2 teaspoon table salt dissolved in a quart of water), which is the general limit of palatability. Severe cases respond rapidly to intravenous isotonic (0.9% NaCl) or small amounts of hypertonic (3% NaCl) saline. Salt

tablets are gastric irritants and should not be taken on an empty stomach.

Heat Edema

Swollen feet and ankles are often reported by nonacclimatized individuals, especially the aged, who encounter climatic stresses of tropical and semitropical areas. Such individuals often have no underlying cardiac, hepatic, venous, or lymphatic disease. They frequently have assumed vigorous schedules with long periods of sitting or standing. The edema is usually minimal, not accompanied by any significant impairment in function, and often resolves after several days of acclimatization. Since this entity is of inconsequential clinical importance, detailed assessment of its pathophysiology is lacking. It is presumed that hydrostatic pressure and vasodilation of cutaneous vessels, combined with some degree of orthostatic pooling, lead to vascular leak and accumulation of interstitial fluid in the lower extremities. Simultaneously, there may occur increased aldosterone in response to heat stress and perceived central volume deficit. Normally, muscles in the legs act as a "second heart" and in concert with venous valves counteract orthostatic pooling, promote venous return, and resist syncope. In fact, intramuscular pressure is higher in non-fainters.

The most important reason for awareness of this clinical presentation is to prevent overly vigorous diagnostic and therapeutic intervention. Brief diagnostic evaluation to rule out thrombophlebitis, lymphedema, or congestive heart failure is

appropriate, but invasive diagnostic techniques or vigorous pharmacologic therapy are not indicated. There is no evidence that diuretic therapy is effective. Rather, simple leg elevation or thigh-high support hose should be employed. In the majority of individuals, benign neglect is the order of the day, as the problem will resolve either through adequate acclimatization or with the individual's return to his climate of origin.

Heat Syncope

Syncope is a perplexing disorder, because a host of serious and even larger number of nonserious underlying mechanisms can result in temporary loss of consciousness. The elderly seem to have a special predilection for this disorder. Individuals adapt to a hot, humid environment by dilating cutaneous vessels to deliver heat to the body surface. Thus, an increased portion of the intravascular pool is located in the periphery at any given time. Increasing blood flow to compliant cutaneous veins raises skin vascular volume at the expense of thoracic blood volume. Individuals who stand for protracted periods of time tend to pool blood in the lower extremities due to gravitational forces. Combined with volume loss and peripheral vasodilation, this may result in inadequate central venous return, a concomitant drop in cardiac output, and cerebral perfusion inadequate to maintain consciousness. The disorder is self-limited, since assumption of a horizontal position is the cure. Unfortunately, individuals may injure themselves in a fall. Skull, cervical spine, and hip injuries must be anticipated in such individuals.

Individuals at risk for heat syncope should be warned to move frequently, flex leg muscles repeatedly whenever standing stationary, avoid protracted standing in hot environments, and assume a sitting or horizontal position whenever prodromal warning signs or symptoms occur. Scintillating scotomata, tunnel vision, vertigo, nausea, diaphoresis, and weakness are prodromal symptoms of syncope. Adequate education will prevent many serious injuries. While adequate oral volume replacement may prevent some cases, prophylactic positioning under these conditions is the most important therapeutic measure. Support hose may be of use to prevent peripheral venous pooling.

HEAT EXHAUSTION

Heat exhaustion (heat prostration) is characterized clinically by weakness, fatigue, frontal headache, impaired judgement, vertigo, thirst, nausea and vomiting, and occasionally muscle cramps. Orthostatic dizziness and syncope may occur. The core temperature is usually only moderately elevated (less than 40° C [104° F]). Heat exhaustion may be differentiated from heat stroke by the modest elevation of core temperature, lack of severe central nervous system pathology such as coma, and lack of elevation of hepatic transaminases invariably seen in heat stroke.[25]

The two types of heat exhaustion classically described are water depletion and salt depletion. Water depletion heat exhaustion results from inadequate fluid replacement by persons working in a hot environment, usually laborers, athletes, military personnel, or invalids without access to water. Persons working in the heat almost

never voluntarily drink as much water as they lose and replace approximately two-thirds of net water loss.[139] This phenomenon, termed "voluntary dehydration",[148] has been noted by many observers. Inadequate fluid intake results in progressive dehydration and hypernatremia, steadily rising core temperature, elevated pulse rate, declining sweat rate, and the central nervous system symptoms noted above. Left untreated, water depletion heat exhaustion will progress to heat stroke.

Salt-depletion heat exhaustion was originally described by McCance[114] and takes longer to develop than does the water depletion form. It occurs when large volumes of thermal sweat are replaced by adequate water, but too little salt. It differs from heat cramps in that systemic symptoms occur. The primary distinguishing factors are hyponatremia, hypochloremia, and low urinary sodium and chloride concentrations. The symptoms are similar to those seen with water-depletion heat exhaustion. Body temperature usually remains near normal.

Pure forms of heat exhaustion are rare. Most cases of heat illness involve mixed salt and water depletion.[70,112] Heat exhaustion is primarily a volume depletion problem, and rapid recovery generally follows fluid administration. Decisions regarding the type of fluid and electrolyte replacements should be based on serum electrolyte measurements and estimation of hydration by laboratory (BUN and hematocrit changes) and clinical (blood pressure, pulse, orthostatic changes, urine output) parameters. In mild cases rest in a cool environment and oral electrolyte solution, such as 0.1% saline, may

suffice. Patients with significant electrolyte abnormalities generally require intravenous fluids. Water deficit in hypernatremic patients may be calculated easily by the formula:

$$\text{Water deficit in liters} = \text{total body water or } [0.6 \times \text{weight in kg}] - \left(\text{total body water} \times \frac{\text{desired } [Na^+]}{\text{measured } [Na^+]}\right)$$

In a 70 kg man with a measured serum sodium $[Na^+]$ of 165 mEq/liter:

Total body water (TBW) = 70 kg x 0.6 = 42 kg = 42 L

$$TBW - \left(TBW \times \frac{\text{desired } [Na^+]}{\text{measured } [Na^+]}\right)$$

$$42\ L - \left(42\ L \times \frac{140\ mEq/liter}{165\ mEq/liter}\right)$$

$$42\ L - 35.6\ L$$

$$6.4\ L$$

If the patient is orthostatic, normal saline should be administered until the patient is hemodynamically stable. Following volume restoration, free water deficit should be calculated as demonstrated above and replaced (over at least 48 hours) so as not to decrease serum osmolality at a rate greater than 2 mOsm/hour.[162] Overly rapid correction of hypernatremia is associated with seizures, apparently due to cerebral edema.[64]

HEAT STROKE

Heat stroke is a syndrome which occurs when homeostatic thermoregulatory mechanisms are unable to meet the demands of heat stress. This failure results in elevation of body temperature to

extreme levels (usually greater than 41° C [105.8° F]), producing multi-system tissue damage and organ dysfunction.

In the majority of cases (80%) the onset of heat stroke is sudden[82,167] and the patient becomes delirious or comatose. Prodromal symptoms lasting minutes to hours occur in approximately 20% of cases. These include weakness, dizziness, nausea, vomiting, anorexia, frontal headache, confusion, drowsiness, disorientation, muscle twitching, ataxia and signs of cerebellar dysfunction, and psychiatric symptoms ranging from irritability and anxiety to psychosis.[10,53,82,102,166]

Classic manifestations of heat stroke include hyperpyrexia, profound central nervous system dysfunction, and hot, dry skin.[93] Absence of sweating is a dramatic finding in a hyperpyrexic patient and has led some observers to theorize that cessation of sweating is a primary factor in the development of heat stroke.[163,182] This "sweat gland fatigue" was postulated to occur due to rising venous pressure.[50] Direct thermal damage has also been suggested.[99] Subsequent observers demonstrated persistent sweating with no signs of thermal damage to sweat glands in patients with rectal temperatures between 41.5 and 42.4° C (106.7 to 108.3° F) and early manifestations of heat stroke.[47] In exertional heat stroke, sweating persists in up to 50% of cases.[94] Therefore, sweat gland fatigue (hidromeiosis) is probably not due to heat stroke, but rather to swelling of sweat gland ducts following chronic exposure to salt and water. This may be the cause of "prickly heat." The presence of sweating does not preclude the diagnosis and cessation of sweating is not always the cause of heat stroke. Core temperature is classically elevated to 41° C (105.8° F) or higher;

however, significant cooling may occur in the prehospital phase, and the first temperature obtained may not represent the original maximum.[25] Shibolet[166] reported typical cases of heat stroke with initial rectal temperatures of 39.5° C (103° F). Thus, reliance on the measured temperature and "classic" features of heat stroke will lead to significant underdiagnosis. The diagnosis should be considered whenever signs of central nervous system dysfunction occur in environmental conditions conducive to heat illness.

DIFFERENTIAL DIAGNOSIS

Heat stroke may be confused with other disorders, particularly central nervous system infections with fever and altered mental status. Cerebral malaria caused by falciparum malaria, which presents a clinical picture of high fever and brain damage, is seen in tropical climates where heat illness may occur. Thick and thin blood smears should be examined looking for malarial parasites if patients have been in an endemic area (see Chapter 30). Shaking chills should suggest fever with altered hypothalamic set point, rather than heat illness. Meningitis and encephalitis may masquerade as heat stroke; a lumbar puncture is helpful in such cases. In heat stroke, the spinal fluid should be crystal clear with occasional lymphocytic pleocytosis or elevated protein levels up to 152 mg/dL.[7,166]

Drug-induced heat illness is an important consideration; substances causing hyperpyrexia have been discussed earlier in this chapter. It is particularly important to diagnose anticholinergic poisoning, since a specific antidote, physostigmine, reverses

anticholinergic poisoning and lowers body temperature.[154] Differentiation may be difficult, since both heat stroke and anticholinergic poisoning may produce hyperpyrexia, hot and dry skin, tachycardia, and central nervous system dysfunction. To compound the difficulty, anticholinergics are frequently not detected on drug screens.[191] However, Khogali[82] states that constricted and pinpoint pupils are present in 69% of heat stroke patients. Mydriasis should be present with anticholinergic poisoning; its absence argues strongly against this diagnosis.

Typhoid fever, typhus, delirium tremens, and hypothalamic hemorrhage have all been reported to cause symptom complexes similar to heat stroke. When a complex differential diagnosis defies precise definition on purely clinical grounds, measurement of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) may be helpful. In most febrile states which present with mental aberration or coma, these enzymes will be normal or minimally elevated, while they are usually significantly elevated early in the course of heat stroke. While not pathognomonic, these elevations may help in confirming a suspected case of heat stroke.[25]

CLASSICAL VERSUS EXERTIONAL HEAT STROKE

It is useful to subdivide heat stroke victims into two forms which have significantly different presentations and manifestations: classical (epidemic) heat stroke (CHS) and exertional heat stroke (EHS). The major differences between the two forms are shown in Table 2.

Classical heat stroke occurs during periods of sustained high ambient temperatures and humidity, such as those which occur during summer heat waves.[7,54,60,184] The victims are usually aged and poor, and live in poorly ventilated homes without air-conditioning. Debilitated patients who do not have ready access to water to replace extensive sweat losses may develop water-depletion heat exhaustion which progresses to heat stroke if untreated.[94] Classical heat stroke victims frequently have chronic diseases, alcoholism, or schizophrenia which predispose to heat illness. Such patients are often prescribed medications such as diuretics, antihypertensives, neuroleptics, and anticholinergics which impair ability to tolerate heat stress. Sweating was totally absent in 84-100% of patients with CHS reviewed in three series.[7,43,104]

In contrast, patients with EHS are usually young and healthy individuals whose mechanisms to dispel heat are overwhelmed by endogenous heat production. Athletes[89,117] and military recruits[14,110] are typical victims. Rhabdomyolysis and acute renal failure, rarely seen in CHS, are common in EHS.[89] Sweating is present in half the cases of EHS.[89] Hypoglycemia occurs[34] as the result of increased glucose utilization and hepatic damage resulting in impaired gluconeogenesis.[76] Coagulopathy is frequent.[167]

PATHOPHYSIOLOGY OF HEATSTROKE: A SYSTEMIC AND CELLULAR APPROACH

Since controlled human experimentation is precluded by risk and because of the uncertainty surrounding animal-to-man extrapolations, the pathophysiology of heatstroke remains speculative. Certain features, however, are readily apparent and new concepts have been

presented which await experimental evaluation.[71]

Systemic Manifestations of Heat Stroke

Collapse or the inability to maintain normal activity is a common feature of heat illness, varying in severity from mild hypotension and fainting with heat syncope to confusion, irrational behavior, and coma with heat stroke. The occurrence of significant heat morbidity and mortality in sports, industry, and military training emphasizes the combined threats from upright posture, environmental heat stress, hypohydration and exercise upon cardiovascular and thermoregulatory homeostasis. Depending upon the intensity and duration of the exercise and the resultant hyperthermia, cardiovascular compensation begins to fail. At some point the individual ceases to work or collapses with one of the characteristic heat illnesses.

A normal functioning central nervous system (CNS) is required to integrate thermal inputs and to initiate appropriate thermoregulatory responses. An intact cardiovascular system transports excess heat from the core to the periphery. Dysfunction within both systems leads to the symptomatology.[167] Failure of either has been cited as the primary cause, but system failures are more often a consequence, rather than a cause, of heat accumulation in a previously healthy individual exercising in a hot environment.

A rise in skin temperature reduces the thermal gradient between the core and the skin and evokes an increase in skin blood flow (peripheral vasodilation). This reduces total vascular resistance, and functional hypovolemia is avoided by a compensatory vasoconstriction of the splanchnic and renal circulations and nonexercising muscle. During

this phase, mean arterial pressure is relatively stable, but with continued effort tachycardia develops because the compensation is not perfect. An increase in plasma norepinephrine and a decline in splanchnic flow are evident at a heart rate of 100 beats per minute.[151] A rise in plasma norepinephrine parallels the rise in heart rate and relative oxygen uptake and is reciprocally related to splanchnic blood flow. The resulting sustained splanchnic and renal ischemia may explain the nausea, diarrhea, and vomiting observed in post-marathon runners.[119]

With prolonged exercise in the heat, a progressive increase in skin blood flow displaces blood volume into cutaneous veins. Combined with a shift of blood volume into dependent limbs, this lowers cardiac filling pressure and stroke volume. Heart rate must increase to maintain cardiac output. Patients with heat stroke usually display tachycardia (up to 180 beats per minute). Normally, excessive cutaneous vasodilation is corrected by baroreflexes. However, when core temperatures and skin blood flow become very high, cutaneous and splanchnic arterioles are unable to constrict enough to prevent venous pooling and a fall in blood pressure. Therefore, in some individuals, blood pressure falls in proportion to increased total vascular conductance. In other individuals increased splanchnic conductance in response to continued heat stress could precipitate an unexpected fall in skin blood flow. Under conditions of constant work, this failure to perfuse the skin with heated blood from the core results in an increased rate of heat storage. Cutaneous blood flow decreases drastically as exhaustion approaches during exercise in the heat.[9]

Rats often display a drastic initial peripheral temperature drop that coincides with an explosive rise in core temperature just prior to exhaustion.[68] A spiralling increase in rectal temperature during prolonged physical effort has been observed with humans with both high and low physical performance characteristics.[67] This sudden rise in core temperature coinciding with a fall in skin temperature signals that underlying splanchnic compensations have failed and exhaustion or collapse is imminent.

Under conditions of increasing hyperthermia, a sudden collapse in an otherwise heat tolerant individual indicates CNS dysfunction and the onset of coma. Since the brain stores little energy, it is dependent upon a constant supply of both oxygen and glucose. Recent experiments with conscious rabbits exposed to an ambient temperature of 40° C (104° F)[168] demonstrate that cerebral edema and cerebral vascular congestion occur concurrently with hyperthermia. At the onset of heat stroke (i.e., coma), intracranial pressure increases which, in combination with the reduction in mean arterial blood pressure, conspires to produce a fall in cerebral perfusion pressure. Decreased cerebral perfusion pressure results in cerebral ischemia and acidosis. The extent of cerebral damage from ischemia, acidosis, and high temperature depends upon the severity and duration of the insult.

The Cell in Heat Stroke

The concept that heatstroke develops whenever "body temperature in itself becomes a noxious agent"[47] is a message without a mechanism. By focusing on the cell, we attempt to take our understanding of this illness beyond the clinical criteria we use to define it. A list of

the hypothetical characteristics of a cellular site has been compiled (Table 3) which attempts to identify the location where the physical effects of heat stress are translated into the physiological manifestations of heat strain.[72] The key factors in this concept act to increase the permeability of the cell membrane to sodium ions and thus produce an added energy drain upon the cell.

Many factors combine to increase intracellular sodium and drive the sodium pump in a hyperthermic person. Heat increases the kinetic energy and diffusion of ions in solution and thus increases sodium permeability. Heat increases intracellular acidity (ATP hydrolysis, glycolysis) and this stimulates a Na^+-H^+ exchange. Heat storage is accompanied by hypohydration (sweating and voluntary dehydration), which increases extracellular sodium concentration. This suggests that the hyperthermia of dehydration is in part due to a general increase in cellular heat production from increased sodium pump activity. Heat increases the neural stimulation frequency (nicotinic, cholinergic) necessary to maintain muscle force, and this increases sodium-potassium flux across cell membranes of stimulated muscles and innervating nerves. Heat and exercise produce regional ischemia (early splanchnic; late cerebral), which increases regional acidosis and Na^+ flux. Heat and work increase muscarinic and nicotinic cholinergic stimulation autonomically and voluntarily, which increases Na+ flux. Since pumping activity increases approximately in proportion to the third power of the sodium concentration, a doubling of the intracellular sodium concentration would result in an eight-fold increase in ATP hydrolysis.[71] Thus, all of these factors which

stimulate the flux of sodium into the cell increase ATP utilization, heat production, and produce an energy drain upon the organism.[72]

Symptoms of muscular weakness are a common complaint in heat illness patients. Rapid onset of muscle rigidity and rigor mortis are classic features following death in severe, exertion-induced heat stroke.[72] Furthermore, the extensibility of muscle during the development of rigor mortis appears linearly related to muscle ATP content. Iodoacetate inhibits glycolysis and severely depresses ATP production. The stimulation of iodoacetic acid poisoned muscle results in pronounced decrements in both ATP and the total adenine nucleotide content, which correlates with early fatigue and rigor. Muscle phosphorylase deficiency (a disorder of glycogenolysis; McArdle's syndrome) is clinically similar to iodoacetate poisoning.[105] In this disorder, a hyperkinetic circulatory response, premature fatigue and cramping are linked to a metabolic impairment that produces a pronounced decline in the muscle phosphorylation potential.[170] The hyperkinetic circulation and increased pulmonary ventilation are thought to be mediated by vasoactive substances (adenosine, K+, etc.) released from muscle and acting on metabolically sensitive skeletal muscle afferents.[105] We have recently reviewed[72] some of these intriguing observations, which suggest that the flux of substances across the cell membrane is intimately related to the cellular energy state and to alterations in homeostatic mechanisms. A full discussion is beyond the scope of this review, but a potential mechanistic relationship exists between heat storage, membrane permeability, stimulation of glycolysis, cellular energy depletion and injury.

This theory had its roots in the observation that in a non-sweating animal model, heating rate was significantly and inversely related to treadmill performance.[71] In other words, the heat the cell sees (i.e. stored heat) adversely affects performance or increases fatigue. Drugs that worsen the cellular energy state through increased neurotransmitter stimulation (physostigmine) or reduced oxidative efficiency (DNP) extend this relationship.

Whereas in McArdle's syndrome, the energy state is lowered by exercise and a substrate deficiency (impaired glycogenolysis), in our model of heat stroke the cell is overwhelmed by an increased energy demand. The "accelerator" of this process is the rate at which sodium "leaks" into cells. This leak rate is seen to have significant autogenerating or positive feedback potential, as shown in Figure 1. We have diagrammed this dynamic relationship between the rate of heat gain, increased membrane permeability, cellular energy depletion, and increased neurotransmitter activity as a vicious circle leading to reduced heat/exercise tolerance and significant morbidity and mortality.

The ultimate outcome of this proposed pathophysiological mechanism would depend on many factors, such as the duration, intensity, and rate of heating, as well as variations in regional and local circulation within the affected tissue. Without a doubt, the cascade begins with heat, is accelerated by acidity, and is progressively worsened with hypohydration. This fits comfortably within the framework of clinical experiences and provides a clear, rational basis for the importance and urgency of cooling to reduce the source of excessive metabolic rate and heat production (i.e. sodium flux). This is consistent with the

recognition by neuro- and cardiovascular surgeons that hypothermia provides clinical protection from circulatory arrest by lowering the basal metabolic rate. Cooling restricts Na^+ channels, delays energy depletion and K+ efflux, and stabilizes the cell membrane.[71] The mechanism supports the essential nature of body cooling as a primary form of treatment.

Secondly, the mechanisms outlined by the model reinforce the importance of acid/base balance in diagnosis and treatment. Although blood lactate levels in exertional heat stroke and in severe exercise do not appear predictive of patient outcome, in classical, non-exertional heat stroke, modest elevations in blood lactate correlate with permanent neurological deficits and death.[60] The reciprocal relationship between lactate levels and probability of survival of circulatory shock are well described.

Thirdly, the systemic importance of pressure/volume relationships clearly has its counterpart in regional ischemia, hyperthermia and the basic underlying problem of Na^+ concentration and flux. This emphasizes the interdependence of many of these variables on the outcome. The deterioration of the cellular energy state in ischemia causes the initiation of dissipative ion fluxes, metabolic cascades and reactions leading to irreversible cell damage.[170] For example, depletion of adenine nucleotides by deamination and dephosphorylation pathways can lead to substrates for free radical formation thought to be destructive to membranes and endothelial cells. Xanthine oxidase, a major source of free radicals, is formed in high concentrations in liver, intestine and lungs.[115] The liver is a prime target for heat stroke damage, perhaps through a combination of higher temperature,

energy depletion, tissue acidosis, functional ischemia and reperfusion with free oxygen radicals. Hepatocytes along the vascular pole and endothelial lining cells are particularly susceptible. Clearly, this energy depletion model suggests that cellular and metabolic processes initiated during hyperthermia are still operative for some time after a patient's temperature has returned to the normal range with cooling.

ORGAN SYSTEM INVOLVEMENT IN HEAT STROKE

Central Nervous System

Signs of profound central nervous system dysfunction dominate the early course of heat stroke. Delirium or coma are characteristic, but aggressive behavior, hallucinations, decerebrate rigidity, oculogyric crisis, opisthotonos and cerebellar syndromes may occur.[63,96,110,159,166] Focal neurologic deficits are unusual, but hemiplegia has been described in a person with heat stroke.[27] Convulsions are not uncommon, occurring in 26 of 36 patients in Shibolet's series.[166] Convulsions occurred both early and late, and were frequently precipitated by therapeutic maneuvers such as ice water immersion. Profound muscle rigidity with tonic contractions, coarse tremor, and dystonic movements often occur and may mimic seizures.[167] Electroencephalograms are generally normal or show nonspecific changes.[166] Cerebrospinal fluid findings have been discussed previously.

Pathologic changes include cerebral edema, petechiae in the walls of the third and fourth ventricles, and marked cerebellar purkinje cell damage.[110] Clinical signs of cerebral edema include papilledema, which

has been reported in three patients.[51,161,195] Survivors may recover completely or suffer chronic disability in the form of cerebellar deficits, hemiplegia, dementia, and personality changes.[167]

CARDIOVASCULAR SYSTEM

Heat stress creates tremendous demands on the cardiovascular system. Circulatory failure was described by Sir William Osler[136]: "The venous engorgement is extreme, particularly in the cerebrum. The left ventricle is contracted and the right chamber is dilated. The blood is usually fluid. The lungs are intensely congested. Parenchymatous changes occur in the liver and kidneys." Malamud[110] described right-sided cardiac dilatation, as well as subendocardial and subepicardial hemorrhage, occasionally extending into the myocardium in the left ventricle. Degenerative changes, including fragmentation, rupture, and fatty changes of cardiac muscle, were also noted. While such pathologic changes in the heart are frequent, the extent of damage is not sufficient to allow a sole cardiac etiology for the demise of the individual.

O'Donnell[132] measured the hemodynamic indices of eight young patients suffering from exertional heat stroke. All cases were characterized by low peripheral vascular resistance. This effect would be expected as a normal response for heat dissipation; however, it persisted in patients treated with ice water bath and reduction of body temperature to near normal. Persistence of low peripheral vascular resistance led to speculation that tissue injury similar to that seen in post-shock and sepsis states may occur. Seven of these patients

exhibited hyperdynamic states with high cardiac indices; however, one patient had a hypodynamic response characterized by hypotension, elevated central venous pressure, tachycardia, and low cardiac output. When this patient was treated with low dose isoproterenol (1 microgram/min), cardiac index and blood pressure rose dramatically. All eight patients had elevated central venous pressures suggesting that peripheral venous pooling, felt to be a cause of hypotension in earlier animal studies,[36] was not an important factor. However, this conclusion must be tempered by the observation that these patients were treated with ice baths at the field aid station. Hemodynamic observations were recorded following intravenous infusion of lactated Ringer's solution. Stine[176] added a "hypovolemic" category of hemodynamic state, characterized by low vascular resistance, hypotension, diminished cardiac output, and low central venous pressure, but did not cite references. This state was not previously observed in exertional heat stroke; rather, all patients treated with IV fluids and ice bath cooling had elevated central venous pressures and modest fluid requirements averaging 1200 cc over the first four hours.[132] Perhaps in elderly patients, especially those with water depletion, this response may be seen, but it remains speculative. The combination of elevated central venous pressure with right-sided cardiac dilatation suggests right-sided cardiac failure, which is also seen after shock or sepsis.[153] The mechanism of right-sided cardiac failure in heat stroke is unclear; myocardial injury[121] and increased pulmonary vascular resistance[41] have been suggested.

The cardiovascular response to heat stroke in rats may be

characterized by three distinct stages: compensation, crisis, and failure.[84] The "compensation" phase is characterized by peripheral vasodilation and lowered total vascular resistance. Functional hypovolemia is avoided by compensatory vasoconstriction of the splanchnic circulation[36,149] and non-exercising muscle and kidney.[141] The "crisis" is characterized by a hyperkinetic circulation similar to the hyperdynamic state observed by O'Donnell.[132] Gold[50] demonstrated a similar state in human volunteers exposed to dry heat, marked by extremely high central venous pressures. The third murine stage is characterized by cardiac failure heralded by declining mean arterial pressure. The authors surmised, "although circulatory failure could ultimately be ascribed to cardiac failure, the trigger in all probability was the excessive reduction in total vascular resistance following the abolishment of compensatory splanchnic vasoconstriction".[84] A failure in myocardial energy transformation was also postulated.

Sinus tachycardia is present on the electrocardiogram of virtually all heat stroke victims. Bundle-branch blocks, ST and T wave changes, and prolonged QT interval have been described;[34,63,107] such changes are usually rate-related or transient. Although ventricular tachycardia has been reported in heat stroke,[6] ventricular fibrillation, the most feared complication of hypothermia, does not occur as a primary event.

HEMATOLOGIC SYSTEM

Osler[136] observed that "the blood remains fluid" in patients succumbing to heat stroke and Malamud[110] described widespread petechial

and gross hemorrhages involving multiple organ systems. Shibolet[166] called the coagulopathy "one of the grimmest aspects of heat stroke and presumably the cause of death in most fatal cases". Aberrations in coagulation are common in severe heat stroke and their presence is a poor prognostic sign.[166] The etiology is complex and multifactorial. Electron microscopy studies have shown severe capillary endothelial damage with platelet aggregation and widespread micro-thrombi.[173] Such endothelial damage results in release of thromboplastic substances with resultant intravascular thrombosis and secondary fibrinolysis. Hypofibrinogenemia, elevated fibrin split products, and thrombocytopenia indicate the presence of disseminated intravascular coagulation.[166,173,175,188] Heat exposure produces enhanced fibrinolytic activity, which is diminished by acclimatization.[12,122] Primary fibrinolysis and thermal activation of clotting factors has been postulated.[165] Impaired hepatic function results in decreased production of clotting factors.[167] Malamud[110] described depletion and damage of megakaryocytes in the bone marrow, which he attributed to thermal damage. Thrombocytes exposed in vitro to temperatures above 42° C do not aggregate in the presence of ADP or prothrombin and display no clot retraction at 44° C.[194] Decreased survival time of red cells and hemolytic anemia have been described.[57] Thus, an intricate array of pathologic changes may inhibit normal hemostasis in heat stroke victims. These interactions are displayed schematically in Figure 2. Abnormal hemostasis may be manifested clinically by purpura, conjunctival hemorrhage, melena, bloody diarrhea, hemoptysis, hematuria, myocardial bleeding, or hemorrhage into the central nervous

system.[86,166]

GASTROINTESTINAL SYSTEM

Hepatic damage is such a consistent feature of heat stroke that its absence should cast doubt upon the diagnosis.[80] Hepatic injury is evidenced by elevated levels of asparate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH). Levels of AST greater than 1,000 units (normal 10-35) are a poor prognostic factor.[30] Jaundice typically appears 24 to 72 hours after the onset of severe heat stroke, and gradually recedes if the victim survives.[63] Kew[79] described centrilobular necrosis with extensive cholestasis in biopsies from gold miners with heat stroke. Survivors suffer no permanent impairment of liver function. Hypoglycemia with serum glucose below 65 mgZ was noted in 5 of 12 patients with exertional heat stroke.[34] This was attributed to depletion of muscle glycogen and impairment of hepatic gluconeogenesis. Hyperglycemia secondary to catecholamine release has also been described.[56]

Diarrhea is frequently seen and aggravated by cooling;[3] it may constitute an annoying problem. Long-distance runners suffer from diarrhea on warm days.[119] Drastic reductions in intestinal blood flow occur which under these circumstances[149] may explain this observation. Serum amylase levels are typically elevated, and pancreatitis may occur;[94] intense splanchnic vasoconstriction has been postulated as the cause.[140]

RENAL SYSTEM

The initial urine specimen, usually obtained by catheterization

is a scanty, brownish, turbid fluid, resembling "machine oil".[166] Microscopic contamination reveals proteinuria with abundant granular casts and red blood cells.[82] Acute oliguric renal failure complicates 25-30% of exertional heat stroke cases and 5% of sedentary heat stroke cases.[88] Heavy physical exertion in hot climates produces acidic and maximally concentrated urine.[161] In this setting, the added insult of myoglobinuria or hypotension may precipitate acute oliguric renal failure. Rhabdomyolysis and myoglobinuria have been well-documented, and may explain the increased incidence of renal failure in exertional as opposed to classical heat stroke victims.[186] Glomerular filtration rate, renal plasma flow, urine flow, and sodium excretion diminish markedly during exercise.[28] Additional factors may also play a role. Hyperuricemia occurs in response to heavy exercise[130] and urate nephropathy has been postulated.[88] Glomerular damage may occur consequent to disseminated intravascular coagulation.[173] Direct thermal injury has been postulated.[161] Proposed mechaniams of renal damage are summarized in Figure 3.

ELECTROLYTE ABNORMALITIES

In the absence of renal failure, most heat stroke victims tend to be hypokalemic.[7,60,81,167] Intense physical exertion in hot climates leads to stimulation of the renin-aldosterone system, which enhances sodium conservation, but may result in a potassium deficit of 500 mEq over one to two weeks.[87] Potassium deficiency causes muscle injury and rhabdomyolysis,[91] and decreases cardiac output in potassium-depleted dogs.[91] Although these observations could explain rhabdomyolysis and

circulatory failure seen with heat stroke, they are unlikely to be operative in most cases, since significant depletion of potassium takes at least a week of hard work and voluminous sweating, a history lacking in most heat stroke victims. Hyperkalemia may occur in patients who become uremic, usually after the fifth day of illness.[166]

Hypocalcemia, hypophosphatemia, and hypomagnesemia have all been reported in heat stroke patients.[90,184] Hypocalcemia is probably due to calcium phosphate or calcium carbonate deposition in damaged muscle and is also seen with idiopathic rhabdomyolysis.[92] Increased losses of calcium and magnesium in urine and sweat also occur with heat stress.[13] Respiratory alkalosis, common in early heat stroke, may partially explain hypophosphatemia.[90] These changes are transient and treatment is generally not indicated.

ACID-BASE ABNORMALITIES

Respiratory alkalosis is a physiologic response to active or passive heating[46] and may be severe enough to produce tetany in patients with heat stroke.[101] While most patients with classical heat stroke present with respiratory alkalosis,[60] patients with exertional heat stroke usually have a relatively pure lactic acidosis.[34,59,155] Lactic acidosis is common with exhaustive exercise; a lactate level of 32 mmol/L has been observed in a cross-country skier without ill effect.[137] In Costrini's[34] series of 13 Marine recruits with exertional heat stroke, mean lactate level was 14.7 mmol/L and all patients survived without long-term sequelae. In contrast, Hart et al[60] observed that in patients with classical heat stroke, those with

moderate lactic acidosis (mean lactate 5.6 mmol/L) suffered permanent neurologic damage and those with severe lactic acidosis (mean lactate 9.65 mmol/L) died. Thus, lactic acidosis augurs a poor prognosis in classical, but not in exertional heat stroke.

TREATMENT OF HEAT STROKE

Heat stroke is a true medical emergency. Irreversible thermal change may occur rapidly. As Khogali[83] points out, "it does not take long either to boil an egg or to cook neurons". The importance of rapid cooling to below 39° C cannot be over-emphasized.[58] Although initial core temperature does not correlate with outcome, most reviewers feel that the duration of hyperthermia is the most important determinant of ultimate outcome.[88,166] Thus, medical personnel must have a high index of suspicion and consider heat stroke in any case of neurologic dysfunction in conditions conducive to development of heat illness.

THE ABCs

Airway management is critical for resuscitation of any critically ill patient. Aspiration, seizures, and retention of secretions are common.[3] Insertion of a cuffed endotracheal tube provides definitive control of the airway. Hypoxemia may occur due to aspiration, pneumonitis, pulmonary infarction, pulmonary hemorrhage, pulmonary edema, or a combination of these factors.[3,30,110,167] Metabolic demands are high and although there are no data to show that normal pulmonary ventilation is regularly inadequate in this setting,

supplemental oxygen should be administered.[20] Positive pressure breathing is indicated if there is difficulty maintaining full oxygen saturation of hemoglobin with supplemental oxygen alone.

Circulatory support represents a complex clinical problem. Intravenous access should be obtained as quickly as possible. Usually, fluid requirements are modest, averaging 1200 mL. of Ringer's lactate or saline in the first four hours.[132] Pulmonary edema occurs in heat stroke[186] and may be exacerbated by overzealous fluid administration. Insertion of a Swan-Ganz pulmonary artery catheter is indicated whenever necessary to guide fluid therapy. Most patients will show a hyperdynamic circulation with high cardiac index, low peripheral vascular resistance, and potentially elevated central venous pressure secondary to right heart failure.[132] These patients require only modest intravenous fluids, since cooling produces vasoconstriction and will increase blood pressure. Occasionally patients exhibit hypodynamic responses with low cardiac index, elevated central venous pressure and hypotension; low-dose continuous isoproterenol infusion (1 microgram/min) resulted in dramatic improvement in one such patient.[132] Patients with evidence of hypovolemia with low central venous pressure, low pulmonary capillary wedge pressure, low cardiac output, and hypotension should be given a fluid challenge. If a Swan-Ganz catheter is not inserted, hypovolemic patients may be identified by use of a central venous catheter. However, since central venous pressure may be elevated depending upon the nature of field first aid in both hyperdynamic and hypodynamic states, a central venous catheter may not help to differentiate these patients. One patient with hypodynamic

indices had bluish-gray skin hue prior to cooling, while the patients with hyperdynamic circulations were initially pink.[132] This clinical finding may be helpful in identifying patients who may respond to isoproterenol when a Swan-Ganz catheter is not available.

The use of alpha-adrenergic drugs such as norepinephrine is not recommended, since they promote vasoconstriction without improving cardiac output or perfusion, decrease cutaneous heat exchange, and perhaps enhance ischemic renal and hepatic damage.[30] Atropine and other anticholinergic drugs which inhibit sweating should be avoided.

The bladder should be catheterized to monitor urine flow. Anuria, uremia, and hyperkalemia are indications for early dialysis.[147] Mannitol may be used to promote renal blood flow and prevent renal damage from myoglobinuria. This is done with an initial bolus of 12.5 grams, followed by 12.5 grams mannitol/liter of intravenous crystalloid.[30] A nasogastric tube should be placed and connected to low intermittent suction. Antacids or histamine-2 blockers have been used to prevent gastrointestinal bleeding; however, no studies exist to demonstrate their efficacy in hyperthermic patients.

COOLING

Cooling is the cornerstone of treatment and must be initiated as soon as possible.[30,58,89,167] Mortality increases significantly when cooling is delayed.[174,198] Cooling efforts should precede any time-consuming search for the etiology. The patient should be removed from the initiating hot environment. Cooling should begin in the prehospital phase by fanning the victim while keeping the skin wet.

When the patient arrives at the hospital, clothes should be removed. Depending on the available equipment, an esophageal or rectal thermistor probe should be placed, and temperature should be noted every 5 minutes. When temperature reaches 39° C (102.2° F), cooling measures should be modified to avoid hypothermic overshoot. Careful, continued monitoring is necessary to detect rebound hyperthermia and to maintain core temperature at 37-38° C (98.6 - 100.4° F).

COOLING MODALITIES

The most widely-used method is immersion in a tub of ice water. Because of the excellent thermal conductivity property of water, this method results in most cases in rapid reduction of core temperature to less than 39° C (102.2° F) within 10 to 40 minutes.[34] In 13 heat stroke victims with initial rectal temperatures greater than 41.1° C (106° F), the mean rate of cooling was 0.16° C/min. This compares favorably to the 0.13° C/min. cooling rate which can be derived from a second clinical report describing cold water immersion.[132] Vigorous skin massage to maintain cutaneous circulation has been advocated; however there is no objective evidence that this is efficacious or necessary. Excellent results have been obtained with immersion. In three military series comprising a total of 66 patients with exertional heat stroke treated with ice water immersion, there were no fatalities or permanent sequelae.[14,34,131] A mortality rate of 14% was reported in a recent series of 28 patients with classical heat stroke treated in this manner.[60] Recent clinical observations and animal experiments[109] suggest that body cooling may occur at a nearly equal rate in water

having a temperature of 15-16° C (59-61° F). Cold water renders the cooling procedure less uncomfortable than iced water immersion to both patients and attendants.

An alternative method of cooling has been developed by Khogali and associates,[190] which utilizes evaporative cooling from the warm skin. In the Makkah body cooling unit, a victim lies suspended on a net surface, while sprayed with atomized 15° C (59° F) water from above and below. Air warmed to 45-48° C (113-118° F) is blown over the skin surface at 3 m/min. The unit is designed to maximize evaporative cooling by maintaining cutaneous vasodilation and avoiding shivering. This results in a 0.3° C (0.6° F) drop in core temperature every five minutes.[83] In clinical trials involving 18 heat stroke victims, 8 were cooled in an hour or less, 5 took 60 to 90 minutes to cool, and the remaining 5 patients took 2-5 hours to cool.[81] In our interpretation of the data, a mean cooling rate of 0.31° C/min. was reported for six mildly hyperthermic (103.1° F) volunteers. In the aforementioned group of 18 heat stroke victims, the mean rate of cooling assessed from rectal temperature measurements was 0.044° C/min. and in another report was 0.046° C/min. These rates are so much lower than those reported for volunteers monitored by tympanic membrane temperatures[190] or for heat stroke patients immersed in ice water[33,131] as to raise questions about the validity of the method, the use of tympanic membrane temperature, or the accuracy of using healthy and mildly hyperthermic subjects to represent heat stroke victims.

The principle of atomized warm water and air movement to maximize evaporative heat loss may be utilized with less elegant equipment. One

group[54] sprayed patients with tepid 40° C (104° F) water from a shower while wind from a standing fan was directed onto the patient. Ice was applied to the lateral aspects of the trunk. This combination produced cooling in 34 to 89 minutes (median, 60 minutes) in 14 patients with classical heat stroke; there was only one fatality.

In support of the Makkah body cooling unit, Khogali[83] cites seven objections to ice water immersion: 1) intense peripheral vasoconstriction shunting blood away from the skin and perhaps causing a paradoxical increase in core temperature, 2) induction of shivering which may increase heat production significantly above basal level,[20] 3) extreme discomfort to the patient, 4) discomfort to the medical attendants, 5) difficulty performing cardiopulmonary resuscitation, 6) difficulty monitoring vital signs, and 7) unpleasant and unhygienic conditions should vomiting and diarrhea occur. However, no one has yet documented paradoxical increase in core temperature following ice water immersion. O'Donnell[132] demonstrated the persistence of decreased peripheral vascular resistance despite ice-bath cooling to normothermia, similar to the post-shock[180] and septic[197] responses. Some argue that vasoconstriction from ice water immersion is beneficial in hypotensive patients[135] and may have aided two hypotensive diabetic patients who died in Khogali's[81] series. Shivering has not been a problem in some groups of patients treated with ice water immersion.[34] It has been treated successfully with chlorpromazine.[14] It is unusual for a heat stroke victim to require cardiopulmonary resuscitation; therefore, this is not a serious limitation of ice-bath treatment. It is our opinion that although cold or ice water immersion may at times

be technically difficult, it clearly is efficacious and saves lives. Warm air spray is comparatively ineffectual for victims in shock with poor peripheral circulation.

The method employed to treat heat stroke victims depends upon the resources available. Written protocols are very helpful and strongly recommended. A list of cooling modalities is shown in Table 3. Application of ice packs is frequently employed; although neater than cold water immersion, this method sacrifices the conductive cooling power of water immersion, resulting in slower cooling (one to three hours) and perhaps higher mortality (24% in one series[166] of young patients with exertional heat stroke). Cooling blankets may be a useful adjunct, but would not produce rapid cooling if employed exclusively. Cardiopulmonary bypass with a heat exchanger has been used successfully in the treatment of malignant hyperthermia.[157] Peritoneal dialysis with cold fluids has been successful in dogs.[24] Cold water gastric or rectal lavage would not be expected to provide significant heat exchange if utilized as the primary cooling modality. Since the pathophysiology of heat stroke and fever differs, antipyretics such as aspirin and acetaminophen are not indicated and may be harmful. Salicylates, particularly in large doses, may worsen hyperthermia by uncoupling oxidative phosphorylation,[160] and aggravate bleeding tendencies. Large doses of acetaminophen could aggravate hepatic damage. Alcohol sponge baths are not recommended, particularly in small children, since alcohol is absorbed through dilated cutaneous blood vessels, producing isopropanol poisoning and deep coma.[116]

ADJUNCTIVE MEASURES

Cooling modalities which drastically lower skin temperature may induce violent shivering, which increases metabolic heat production and may impede cooling. In this situation, chlorpromazine (25-50 mg intravenously) has been efficacious.[75] Chlorpromazine has anticholinergic properties which may interfere with sweating, and may itself occasionally cause hypotension or precipitate convulsions.[88] Chlorpromazine should be used only in instances where cooling is not adequate due to vigorous shivering.

Many patients will be quite agitated during the initial cooling period, particularly if immersed in a tub of ice water. Intravenous diazepam may be used for sedation and to control seizures.[81] Gottschalk[52] recommends barbiturates for treatment of seizures and cautions that metabolism may be altered by hepatic dysfunction. Patients with seizures are at high risk for aspiration and endotracheal intubation is indicated.

Administration of mannitol in an initial IV dose of 12.5 g, followed by 12.5 g mannitol per liter of IV crystalloid, has been advocated to promote renal blood flow and diuresis and hopefully minimize renal damage from myoglobinuria.[30] Mannitol (1 g/kg over 15-20 minutes) has been used to treat cerebral edema. Maintenance of urine flow at a rate of at least 50 ml/hr and urinary alkalinization are indicated[88] as soon as myoglobinuria is documented. The use of dextran is not advised, due to its propensity to coat platelets and impair coagulation.[100] Anuria, uremia, and hyperkalemia are indications for peritoneal or hemodialysis.[147]

Disturbances in blood coagulation may occur during the first day of illness, but are more common on the second and third days.[167] Initial treatment of coagulopathy should be replacement therapy with fresh frozen plasma and platelets.[167] If laboratory signs of disseminated intravascular coagulation (hypofibrinogenemia, elevated fibrin split products, prolonged prothrombin time, thrombocytopenia) are present, intravenous heparin (7500 u every 4 hours) has been efficacious.[188] Although its use should be considered when there is clinical evidence of hemorrhage,[94] the use of heparin for DIC remains controversial. The bleeding tendency in heat stroke may be due in part to fibrinolysis. Although epsilon-amino caproic acid is recommended for fibrinolysis, administration of this compound has been associated with rhabdomyolysis[144] and its use is not recommended in heat stroke.[94]

Both hypoglycemia[34] and hyperglycemia[56] have been reported in heat stroke. Therefore, any patient with altered mental status should have blood glucose checked by a rapid "finger-stick" method or receive a trial of 12.5-25 gm dextrose intravenously.

The use of steroids in heat stroke victims has not been helpful and experimental evidence does not support the need for steroid therapy.[167]

PREVENTION

Prevention of heat illness is a crucial issue. Persons with any risk factor should be counseled regarding symptoms and prevention of heat illness.

Elderly patients and persons with chronic disease or on medications predisposing to heat illness are prone to develop classical heat stroke during periods of high ambient heat and humidity. If air conditioning is not available, fans are quite helpful. Adequate fluid intake is essential; bedridden patients should have free access to water and be encouraged to drink. Bathing or showering in tepid water provides rapid cooling and is available to almost everyone. Elderly patients may dress inappropriately for hot weather; heat loss will be maximized by light, loose fitting garments.

Exertional heat stroke is most likely to occur in young, healthy persons involved in strenuous physical activity. Many of these persons have risk factors for heat illness, commonly obesity, febrile illness, or diarrhea.[11,14] Other variables which should be considered include hydration, salt intake, clothing, and climatic conditions.

Fluid intake is the most critical of these. Persons working in the heat never voluntarily drink as much fluid as they lose and replace approximately two-thirds of net water loss.[139] This dehydration may be minimized by three methods: education on work rest cycles and fluid consumption, provision of cool fluids, and provision of pleasantly-flavored fluids.[69]

Which liquid should be used to maximize fluid intake? The goal is to maximize voluntary intake and gastric emptying, so that fluid may rapidly enter the small intestine where it is absorbed. Gastric emptying is accelerated to 25 ml/min by large fluid volumes (500-600 ml) and cool temperature (10-15.8° C [50° - 60° F]) (Ryan 1975). Soldiers under conditions of heat stress provided with cool, flavored

water consume significantly more fluid than those given warm tap water.[69] High osmolality inhibits gastric emptying; osmolality of less than 200 mosm/l is optimal.[25] Drinking an electrolyte solution during exertion does not affect rectal temperature or serum electrolytes,[164] and glucose is not necessary. For practical purposes, cold, perhaps flavored, water or weak electrolyte solutions provide adequate replacement. Most commercially available electrolyte solutions, such as Gatorade ^{R}, contain excessive sugar. Diluting such products to half-strength with tap water has been recommended. Under conditions of heat stress, sweat losses of 2-3 L/hour are not uncommon. One author suggests 400-500 ml prior to exertion, followed by 200-300 ml at 20-minute intervals during exertion as minimum fluid replacement.[201]

Hydration may be monitored by measuring body weight before and after training or athletic competition; this allows categorization of water deficit by severity.[102] An athlete with a loss of 2-3% body weight (1.5-2 L in a 70 kg man) should be reminded to drink extra fluid and permitted to compete only if he is within 1-2 pounds of his starting weight on the previous day. A weight loss of 5-6% represents a moderately severe deficit and is usually associated with intense thirst, scanty urine, tachycardia, and increase in rectal temperature of about 2° C (3.5° F). Such athletes should be restricted to light workouts after hydration to their normal weight. A loss of 7% or more of body weight represents severe water depletion; the athlete should not participate in sports until examined by a physician.[25,70]

The administration of salt tablets during strenuous exercise may cause delayed gastric emptying, osmotic fluid shifts into the gut,

gastric mucosal damage, and hypernatremic dehydration, and is not recommended. The average salted American diet contains 10-12 grams of sodium per day.[103] Conn[31] demonstrated successful adaptation of men working in the heat with sweat losses averaging 7 L/day on a 6 gram sodium diet. Excessively high salt intake in relation to salt losses in sweat during initial heat exposure may impair acclimatization due to inhibition of aldosterone secretion.[37] Excessive salt ingestion may also exacerbate potassium depletion.[87]

Up to 70% of evaporative cooling may be lost when clothing inhibits air convection and evaporation.[25] Loose-fitting clothing or ventilated "fish net" jerseys allow efficient evaporation. Light-colored clothing reflects rather than absorbs light. Water evaporated from clothing is much less efficient for body cooling than is water evaporated from the skin.

The standard dry-bulb thermometer temperature is a poor predictor of heat illness risk, since it does not take into account humidity, wind velocity, or radiated heat. Tables correlating dry-bulb temperature and humidity are better, but still do not correct for convection or radiation. The most accurate measure of environmental heat stress is the wet-bulb globe thermometer index (WBGT index) which measures three forms of heat load.[120] 10% of the WBGT index is derived from a standard dry bulb thermometer located in the shade. The wet-bulb thermometer is an ordinary thermometer, with a wick surrounding the bulb which is kept moist. As humidity decreases, evaporation occurs in the wick, depressing the wet-bulb temperature below the dry-bulb temperature; the resultant reading comprises 70% of the WGBT

index. The remaining 20% is derived from the unshaded globe temperature reading. A globe thermometer is a standard thermometer inserted with an airtight stopper inside a matte black 6-inch copper ball, and measures radiation from the sun and objects in the area. The resultant WGBT index may be used to predict environmental heat stress and guide activity levels, as shown in Table 4.[25] Use of such an index substantially reduced the incidence of heat illness among Marine recruits at Parris Island.[120] The WGBT index may also be measured by commercially available sling psychometers, which provide economical and simpler approximations of the index.

Despite substantial reductions in heat casualties by use of these measures, heat stroke continues to occur under comparatively mild climatic conditions.[11,167] It is doubtful that all heat stroke cases can be prevented.[11] Thus, physicians caring for active patients in temperate areas must always be sensitive to the possibility of heat stroke and be ready to institute treatment rapidly if significant morbidity and mortality are to be avoided.

Energy Depletion Model

- INCREASED RATE OF NEUROTRANSMITTER OR NEUROMUSCULAR ACTIVITY
- INCREASED RATE OF CELL MEMBRANE DEPOLARIZATION

- REDUCED STEADY-STATE CELLULAR ENERGY LEVELS
- INCREASED LEVELS OF HYPERTHERMIA/DEHYDRATION
- INCREASED SODIUM PERMEABILITY/ Na^+-H^+ EXCHANGE
- CELL SWELLING, FATIGUE, COLLAPSE

- INCREASED RATE OF ENERGY CONSUMPTION/PRODUCTION
- INCREASED RATE OF ION FLUX/PUMPING
- INCREASED RATE OF HEAT PRODUCTION

FIGURE 1

Fig. 1 is Fig. 5 from Hubbard, 1987

(Note: the circle should be repaired by reversing the direction of the left-hand arrow.)

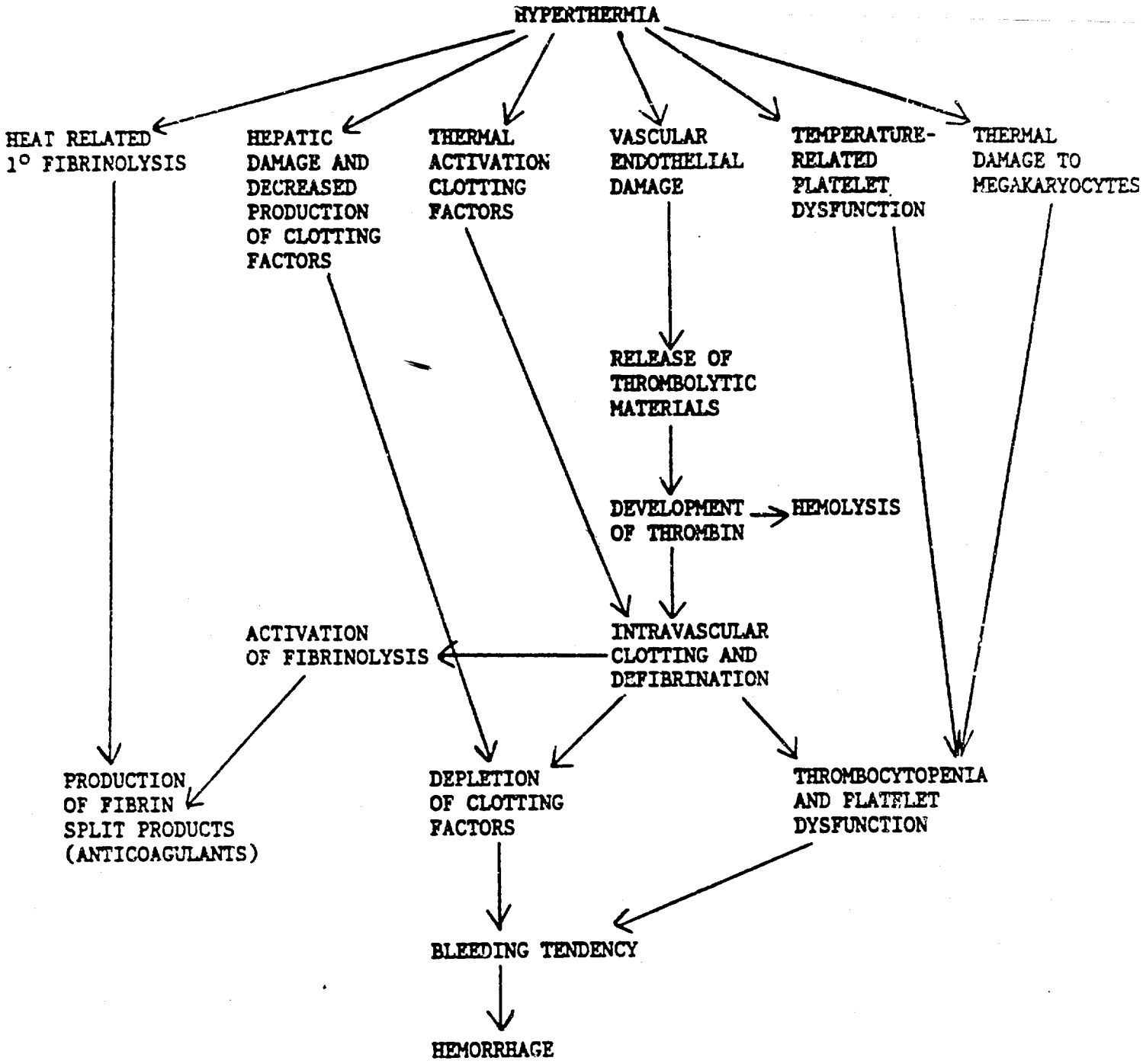

Figure 2: Pathogenesis of abnormal hemostasis in hyperthermia.

HYPERTHERMIA

Splanchnic Vasoconstriction	Rhabdomyolysis		Disseminated Intravascular Coagulation	Thermal Injury
Diminished Renal Blood Flow	Myoglobinuria	Hyperuricemia and Urinary Acidification	Glomerular Damage	

RENAL FAILURE

Figure 3: Pathogenesis of renal failure in hyperthermia.

TABLE 1

Energy Expenditure During Different Activities

Activity	kcal/h
LABOR	
Shoveling	570
Hand sawing	450
Pushing wheelbarrow	300
Carrying bricks	216
Light assembly work	108
Typing	84
SPORTS AND RECREATION*	
Football	102
Wrestling	114
Hockey	173
5-mile run	360
Walking (4 mph)	340
Basketball	344
Swimming	660

*Calorie expenditure per event given as increment above basal requirement.

Source: Knochel[94]

	Classical	Exertional
Age group	Elderly	Men 15-45
Health status	Chronically ill	Healthy
Activity	Sedentary	Strenuous exercise
Drug use	Anticholinergics, diuretics, antipsychotics, antihypertensives, antidepressants	Usually none
Sweating	Usually absent	Often present
Lactic acidosis	Usually absent, poor prognosis if present	Common, may be marked
Rhabdomyolysis	Unusual	Frequently severe
Hyperuricemia	Modest	Severe
Acute renal failure	< 5% of patients	25-30% of Patients
Hypocalcemia	Uncommon	Common
DIC	Mild	Marked
CPK/Aldolase	Mildly elevated	Markedly elevated
Hypoglycemia	Uncommon	Common
Mechanism	Poor dissipation of environmental heat	Excessive endogenous Heat production

Table 2: Comparison of Classical and Exertional Heat stroke, adapted from Knochel.[94]

TABLE 3

Site of Cellular Heat Stroke Injury: Hypothetical Characteristics:

. Common feature of all cells - especially nerves and muscles

· Temperature sensitive

· Related to cell volume changes

· Functionally related to the acclimatization response

· Functionally related to tolerance and fatigue

· Ability to generate heat

· Potential for inducing irreversible change

TABLE 4

COOLING MODALITIES REPORTED TO BE USEFUL IN LOWERING BODY TEMPERATURE IN HEAT STROKE

- Ice water immersion
- Evaporative cooling using large circulating fans and skin wetting
- Ice packs
- Peritoneal lavage
- Rectal lavage
- Gastric lavage
- Cardiopulmonary bypass
- Alcohol sponge baths (caution)
- Phenothiazines (caution)

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